Solid Lipid Nanoparticles (SLN) for Topical Pulmonary Co-delivery of Prostaglandin E and siRNA
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Purpose
In this study, we propose to deliver solid lipid nanoparticles (SLN) containing both prostaglandin E2 (PGE2) and siRNA locally through inhalation for treatment of mice with idiopathic pulmonary fibrosis (IPF).

Methods
SLN were used as a platform to deliver PGE2 and siRNA. Emulsion-ultrasonication technique was used to prepare SLN from tween 80, tween 20, pluronic F68, Precirol ATO5, and Compritol. Nanoparticles were characterized by atomic force, transmission electron (TEM), and fluorescence microscopes. Size and charge of SLN were also analyzed. In vitro study included testing of cyto- and genotoxicity of SLN, PGE2 and siRNA. In vivo experiments were carried out on SKH1 mice. Bleomycin was administered intratracheally to the mice in 1.5 U/kg dose. Mice were treated for 3 weeks with complex SLN by inhalation or intravenous injection. Mice were sacrificed and lungs, liver, kidney, spleen, heart, brain, and serum were collected for histological analysis and blood troponin T levels. In addition, lungs were used for the histopathological evaluation, TEM, immunohistochemistry, immunoblotting and collagen studies. RNA was isolated for further qPCR analysis of 84 key genes involved in the development of lung inflammation and fibrosis. Distribution of liposomes in lungs and other organs after intravenous or inhalation administrations was examined using an IVIS imaging system. In addition to histopathological examination and measurement of hydroxyproline, magnetic resonance imaging (MRI) was used to visualize fibrotic tissues.

Results
It was found that chemokine CCL12, matrix metalloproteinase MM3 and hypoxia inducible factor HIF1 alpha are key pathways responsible for the development of inflammation and IPF. Inhibition of these proteins by the local co-delivery of SLN containing PGE2 and multiple siRNAs targeted to mRNA encoding these proteins led to the suppression of collagen expression, inflammation, fibrotic injury, and prevention of the decrease of body weight and mortality.

Conclusion
Our results demonstrated that IPF can be effectively treated by local inhalation lung delivery of PGE2 and several specific siRNA by stable complex lipid nanoparticles. The data provided evidence that dual drug/siRNA nanoparticle-based inhalation delivery led to the overcoming of fibrogenesis making this composition an attractive medicament for treatment of inflammation and IPF.